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REPLY TO
ATTENTION OF
Military Vaccine Agency

March 18, 2005

Food & Drug Administration
Division of Dockets Management
5630 Fishers Lane
Room 1061
Rockville, MD 20852

SUBJECT: Docket Number 1980N-0208, Final Rule and Final Order Involving Bacterial Vaccines and Toxoids

Ladies & Gentlemen:

Since July 1999, I have served as the Deputy Director for Clinical Operations of the Anthrax Vaccine Immunization Program (AVIP). In this role, I have been responsible for both assessing the rate of adverse events after anthrax vaccinations administered by the Department of Defense (DoD) and encouraging the publication of studies describing the clinical experience of anthrax vaccinees in peer-reviewed medical journals.

First, DoD has a duty to do all it can to help service members who are sick, regardless of why they are sick. The Department of Defense addresses the issue of vaccine safety forthrightly. We vaccinate troops to keep them strong. If vaccines cause problems, we want to know about it so we can stop or modify our vaccination programs.

My colleagues and I have a duty to keep service members healthy to the greatest extent possible. This includes vaccination against preventable infections. We consider ourselves obliged to investigate vaccine-safety concerns openly and vigorously, and to present honest, reliable information for science and the public to use. To fulfill this obligation, we provided or arranged for frank discussions of anthrax vaccine safety during public sessions of the National Academy of Sciences' Institute of Medicine, the Advisory Committee on Immunization Practices, and the Armed Forces Epidemiological Board.

The quality and quantity of the medical evidence bearing on the effectiveness and safety of anthrax vaccine have been reviewed by multiple panels of civilian physicians and scientists. In each instance, the panels have concluded that anthrax vaccine protects people from harmful infection, causing side effects like other vaccines. A list of these panels and the location of their reports appears at Enclosure 1. A comparison of frequent adverse events after various vaccinations, as determined by the National Academy of Sciences, appears at Enclosure 2.

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In listening to people concerned about adverse events after anthrax vaccination, we have seen many individuals make a fundamental mistake in assuming, based on time alone, that adverse events after vaccination were caused by vaccination. These individuals come from all age groups, both genders, and occupations diversely including enlisted service members, military officers, newspaper reporters, physicians, and civic leaders, among others.

This type of oversimplification has been around so long that it has its own Latin phrase: the "post hoc, ergo propter hoc" fallacy (the "it happened after, therefore it happened because of" fallacy). In short, people have a tendency to assume that "after" means the same as "caused by."

America's universities teach that good science is the best way for humans to avoid this pitfall. Any given medical diagnosis occurs at a certain rate in unvaccinated people (i.e., the background rate). If a vaccinated person gets sick with that diagnosis after vaccination, is that diagnosis part of the expected background rate? Or is that person's diagnosis actually due to vaccination?

There are many sources of data that should be taken into account when performing good scientific evaluation. These sources offer varying degrees of objectivity and freedom from bias. Enclosure 3 depicts a relative hierarchy of the reliability and scientific power of these study designs. Each of these study designs contributes to our understanding of the safety of anthrax vaccine.

Some members of the public have written to the FDA, erroneously stating that DoD relies solely on the Vaccine Adverse Events Reporting System (VAERS) to assess vaccine safety. As seen by its position in Enclosure 3, VAERS reports should not be the primary means of assessing vaccine safety. So DoD uses VAERS to identify signals and to act as a patient registry. Then DoD goes further, using cohort studies and other scientifically powerful approaches to assess vaccine safety.

One of the most reliable ways to describe the safety of anthrax vaccine is by using epidemiology, the measurement science of public health, to compare vaccinated and unvaccinated groups of people. If a health problem was truly caused by vaccination, then the rate of disease should be higher in the vaccinated group, compared to the unvaccinated group. If a vaccine causes a health problem, then that health problem would occur more often among vaccinated people than unvaccinated people. That health problem would be occurring at the background rate plus whatever additional rate is attributable to vaccination.

To assess the safety of anthrax vaccination, we started by determining the rates of various hospitalizations among service members who did not receive anthrax vaccine. For simplicity, let's say that 100 unvaccinated service members were hospitalized for a specific cause per year out of a population of 100,000 unvaccinated service members. From that background rate, we naturally would expect 100 anthrax-vaccinated service members to be hospitalized per year out of a population of 100,000 anthrax-vaccinated

service members. No vaccine can prevent unrelated hospitalizations. And this is what occurs in DoD's experience: anthrax-vaccinated people are as likely to be healthy and as likely to get sick as unvaccinated people. The "post hoc, ergo propter hoc" fallacy occurs among people who are surprised or alarmed that the rate of hospitalization is not zero per 100,000 anthrax vaccinees.

But "after" is just one factor to be considered if you want to objectively evaluate "caused by." Enclosure 4 lists the main factors that need to be taken into account in deciding whether a temporal relationship is also a cause-and-effect relationship.

We sometimes hear about people who believe that the long-term effects of anthrax vaccination have not been studied. This is incorrect. As one example, DoD arranged for an evaluation of the effect (if any) of anthrax vaccination on occupational evaluations for disability discharge. The purpose of this study was to identify health problems that might be delayed in appearance after anthrax vaccination or that might have a prolonged effect on physical functioning (Sulsky et al., 2004; see bibliography at Enclosure 5). Researchers evaluated the Total Army Injury and Health Outcomes Database, maintained by the U.S. Army Research Institute of Environmental Medicine, to assess effects of anthrax vaccination between 1998 and 2001. This study evaluated 716,833 active-duty soldiers (154,456 of whom received anthrax vaccine) followed for 4¼ years. The researchers found that rates of evaluation for disability discharge were the same for both vaccinated and unvaccinated personnel (about 4%). Subset analyses found no differences for men alone, women alone, permanent disability, temporary disability, musculoskeletal disability, or neurologic disability.

Another example is the assessment of laboratory workers from Fort Detrick evaluated four decades after their first military vaccinations (Pittman et al., 2004). In that study, 155 workers who received an average of 154 vaccinations or skin tests each between 1943 and 1969 (92% of whom received anthrax vaccine) were compared to 265 community controls from central Maryland. Their average age was 69 years old. The laboratory workers reported fatigue more often than control subjects did, but this fatigue was not associated with number of injections received, number of vaccinations received, or time employed. No differences for self-reported medical conditions between the groups were identified. Several laboratory abnormalities were more common in workers, but none were clinically significant. The authors concluded that intensive vaccination is not associated with an elevated risk of disease or medical condition.

Since July 1999, 20 scientific articles have been published in respected medical journals describing the safety experience of more than 800,000 anthrax vaccinees. Most of these 20 studies are cohort studies that fall in the upper layers of Enclosure 3. Some described months of experience, others described years of experience. Some used control groups, others merely described those vaccinated. Some solicited data from vaccinees; others involved spontaneous submission of data. Some followed vaccinees forward in time; others looked back in a retrospective fashion. Some were authored by military investigators; others were authored by civilian physicians or

scientists. In aggregate, these studies show that anthrax vaccine is basically as safe as other widely used vaccines. In some respects, there is more detailed safety data for anthrax vaccine than for some other commonly used vaccines.

Anthrax vaccine is an aluminum-adjuvanted vaccine given subcutaneously (into tissue about ½" below the surface of the skin). As a result, anthrax vaccination results in more injection-site swelling than most vaccinations. This swelling is temporary. The rates of systemic symptoms (such as headache or malaise) after anthrax vaccination are the same as with other vaccinations (as shown in tables in chapters 4 and 6 of the Congressionally commissioned March 2002 report by the National Academy of Sciences, summarized in Enclosure 2 of this letter).

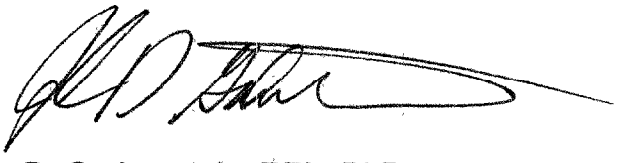
The Department of Defense has clinical and public-health systems in place to identify unrecognized problems after vaccination. The effectiveness of these systems is best exemplified by DoD's discovery of myocarditis after smallpox vaccination in February 2003. DoD clinicians and epidemiologists were the first in the United States to recognize, publicize, and respond to the cause-and-effect link between myocarditis and primary smallpox vaccination.

Had a similar finding of a cause-and-effect relationship between anthrax vaccine and a substantial health problem been found, DoD clinicians and epidemiologists would have publicized and responded to it also. With more than 5.2 million doses of anthrax vaccine given to over 1.3 million people in DoD since March 1998, we have had ample opportunity to find such relationships if they existed. Still, our eyes and ears are open to events that might manifest in the future.

DoD's public-health surveillance systems collect information automatically from all military hospitals and clinics, removing the reporting bias associated with VAERS reports (Lange et al., 2003). Because our surveillance systems systematically collect data on all inpatient and outpatient visits, DoD's surveillance system has advantages over some aspects of surveillance systems in civilian settings. All the encounter records are evaluated; no individual action on the part of the vaccine recipient, physician, or nurse is needed to be part of the surveillance network.

Undoubtedly, there are people within the Department of Defense who got sick after they received anthrax vaccine. Members of the National Academy of Sciences panel on anthrax vaccine listened personally to some of them during its public sessions and read personal accounts from others. DoD has listened to our patients and continues to listen. We do not dispute their illnesses and we endeavor to give our patients the best possible health care. But we are unable to attribute patterns of health problems to anthrax vaccination in a cause-and-effect manner, beyond that which is expected with other FDA-licensed vaccines. In individual cases, we do our best to assess causality, but at the individual patient level, it is the need for excellent patient care that predominates.

To watch out for the health of our troops, DoD uses the modern scientific principles taught in America's best universities. DoD consults with America's best civilian scientists, including members of the National Academy of Sciences, the Advisory Committee on Immunization Practices, and the Armed Forces Epidemiological Board (Enclosure 1). Despite the extensive body of knowledge already published in peer-reviewed medical journals demonstrating the relative safety of anthrax vaccine, DoD continues its safety monitoring program, as is prudent for all vaccines and medications. Vigorous safety monitoring is the right thing for us to do sustain the health and safety of our people.



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Enclosure 1. Civilian Panels That Evaluated Anthrax Vaccine for Effectiveness and Safety

FDA Panel on Bacterial Vaccines and Toxoids, 1978, 1985.

Advisors to the Food and Drug Administration.

Food and Drug Administration. Biological products; Bacterial vaccines and toxoids; Implementation of efficacy review. *Federal Register* 1985;50(Dec 13):51002-117. www.anthrax.mil/media/pdf/Fed_Reg.pdf

Armed Forces Epidemiological Board (AFEB), 1994 to present.

Advisors to the Assistant Secretary of Defense for Health Affairs and the Surgeons General of the Armed Forces.

Recommendations: August 1994, November 1996, April 1998, March 2000, March 2002, www.tricare.osd.mil/afeb/, www.anthrax.mil/resource/library/afeb.asp

Cochrane Collaboration, 1998, 2004.

Demicheli V, Rivetti D, Deeks JJ, Jefferson T, Pratt M. The effectiveness and safety of vaccines against human anthrax: A systematic review. *Vaccine* 1998;16(May-Jun):880-4. www.anthrax.mil/media/pdf/EffandSafety.pdf . Updated in 2004: www.cochrane.org/cochrane/revabstr/ab000975.htm

Working Group on Civilian Biodefense.

Inglesby TV, Henderson DA, Bartlett JG, et al. Anthrax as a biological weapon: Medical and public health management. *Journal of the American Medical Association* 1999;281(May 12):1735-45. jama.ama-assn.org/cgi/reprint/281/18/1735.pdf

Inglesby TV, O'Toole T, Henderson DA, et al. Anthrax as a biological weapon, 2002: Updated recommendations for management. *Journal of the American Medical Association* 2002;287(May 1):2236-52. jama.ama-assn.org/cgi/content/short/287/17/2236

Advisory Committee on Immunization Practices (ACIP).

Advisors to the Centers for Disease Control and Prevention (CDC).

Advisory Committee on Immunization Practices. Use of anthrax vaccine in the United States. *Morbidity and Mortality Weekly Report (MMWR)* 2000;49(RR-15) (Dec 15):1-20. www.cdc.gov/mmwr/PDF/rr/rr4915.pdf

Anthrax Vaccine Expert Committee (AVEC).

Sever JL, Brenner AI, Gale AD, Lyle JM, Moulton LH, West DJ. Safety of anthrax vaccine: A review by the Anthrax Vaccine Expert Committee (AVEC) of adverse events reported to the Vaccine Adverse Event Reporting System (VAERS). *Pharmacoepidemiology & Drug Safety* 2002;11(Apr-May):189-202. www.anthrax.mil/media/pdf/AVEC_ms.pdf

Sever JL, Brenner AI, Gale AD, Lyle JM, Moulton LH, Ward BJ, West DJ. Safety of anthrax vaccine: An expanded review and evaluation of adverse events reported to the Vaccine Adverse Event Reporting System (VAERS). *Pharmacoepidemiology & Drug Safety* 2004;13(Dec):825-840. www.anthrax.mil/media/pdf/SeverArticle.pdf

National Academy of Sciences (NAS), Institute of Medicine (IOM).

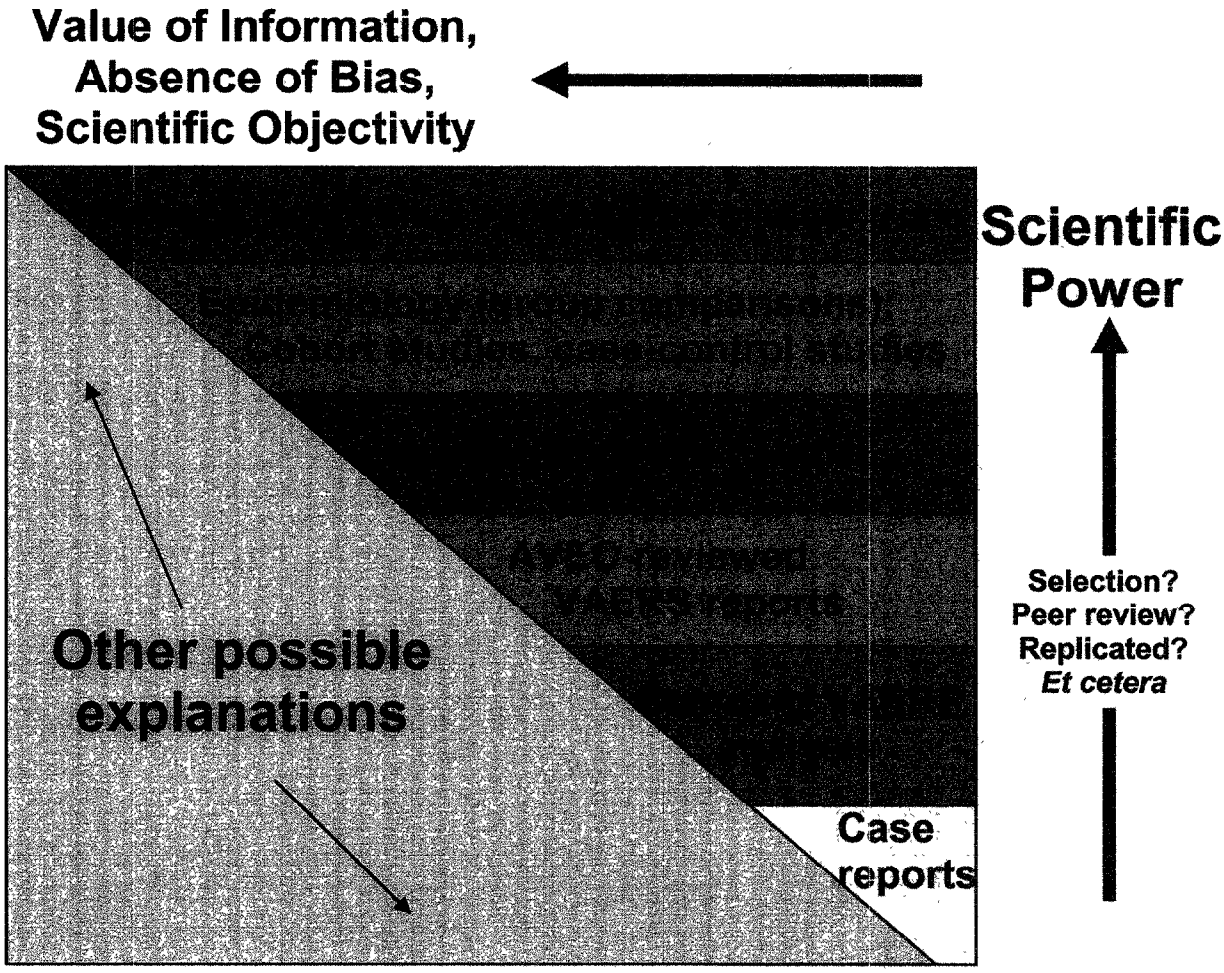
Joellenbeck LM, Zwanziger L, Durch JS, Strom BL, editors. *The Anthrax Vaccine: Is it Safe? Does it Work?* Washington, DC: National Academy Press, April 2002, xxi + 265 pages. www.nap.edu/catalog/10310.html
Summary for General Public: www.iom.edu/Object.File/Master/4/149/0.pdf
Summary for Policy Makers: www.iom.edu/Object.File/Master/4/150/0.pdf

Enclosure 2. Comparison of Common Adverse Events After Various Vaccinations

	Fever	Systemic (beyond injection site)	Redness or Swelling	Pain, Any
Hepatitis A	0 - 3%	4 – 22%	4 - 40%	40 - 52%
Hepatitis B	0 - 4%	10%	1 - 99%	11 - 43%
Influenza	1 - 13%	11 – 34%	11 - 21%	24 - 86%
Pertussis, acellular	0 - 7%	17 – 29%	12 - 15%	51 - 77%
Rabies	2 - 18%	3%	1 - 18%	4 - 52%
Tetanus - diphtheria (Td)	1 - 9%	17 – 26%	22 - 35%	43 - 85%
Anthrax	1 - 8%	1 – 36%	3 - 42%	Sore: 67 - 83%

Source: National Academy of Sciences (NAS), Institute of Medicine (IOM): Joellenbeck LM, Zwanziger L, Durch JS, Strom BL, editors. *The Anthrax Vaccine: Is it Safe? Does it Work?* Washington, DC: National Academy Press, April 2002, xxi + 265 pages. www.nap.edu/catalog/10310.html

Enclosure 3. Hierarchy of Scientific Study Designs and Data Sources



Enclosure 4. Factors To Consider in Evaluating Temporal Relationships for Cause-and-Effect Relationship

A. When Assessing Effects in Populations:

- What is the strength of association (e.g., relative risk, attributable risk) between the exposure (e.g., vaccination) and health outcome (e.g., diagnosis)?
- What is the quality of the clinical or scientific evidence?
- Does a dose-response relation exist?
- Is there consistency among different studies?
- Does the health problem have a specific or unique cause?
- Did the cause exist before the effect began?
- What is the strength of biological plausibility for postulated mechanisms?

B. When Assessing Individual Cases:

Essential criteria:

- Did the exposure (e.g., vaccination) come before the health outcome?
- Was the health outcome confirmed by qualified physician(s)?

Features of the individual case:

- Did the problem recur when the exposure was repeated ("rechallenge")? Did the problem cease when the exposure ceased ("dechallenge")?
- Are other causes of the health outcome unlikely?
- Do any biological markers support a causal relationship?

Supporting factors:

- What is the relative risk between exposed and unexposed populations?
- Do other similar exposures (e.g., other vaccines) cause the same health problem?
- Is the exposure (e.g., vaccination) the only cause of this health outcome?
- What is the strength of biological plausibility for postulated mechanisms?
- Do animal studies support a causal relationship?

Enclosure 5. Bibliography

Lange JL, Lesikar SE, Brundage JF, Rubertone MV. Comprehensive systematic surveillance for adverse effects of anthrax vaccine adsorbed, US Armed Forces, 1998-2000. *Vaccine* 2003;21:1620-28. http://www.anthrax.mil/documents/library/science.pdf

Pittman PR, Coonan KM, Gibbs PH, Scott HM, Cannon TL, McKee KT Jr. Long-term health effects of repeated exposure to multiple vaccines. *Vaccine* 2004;23:525-36. www.vaccines.mil/documents/library/Longtermhealtheffects.pdf

Sulsky SI, Grabenstein JD, Delbos RG. Disability among U.S. Army personnel vaccinated against anthrax. *Journal of Occupational & Environmental Medicine* 2004;46:1065-1075. http://www.anthrax.mil/documents/library/Anthrax2004.pdf